Pathophysiology, Epidemiology, and Natural History of Benign Prostatic Hyperplasia

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The pathophysiology, epidemiology, and natural history of benign prostatic hyperplasia (BPH) are incompletely understood; however, the development of reliable instruments to measure symptom severity, prostatic enlargement, and bladder outlet obstruction has allowed major advances in their elucidation. The development of lower urinary tract symptoms (LUTS) in the aging male is influenced to some degree by the severity of bladder outlet obstruction and prostatic enlargement. Although the development of LUTS, bladder outlet obstruction, and BPH are age-dependent, they are not necessarily causally related; there are many other factors involved in the pathophysiology of LUTS. The clinically important parameters of disease progression in men with moderate to severe LUTS and low peak flow rates are symptom progression and the development of acute urinary retention (AUR). The risk of AUR is related to both baseline serum prostate-specific antigen level and prostate volume. In men with moderate prostate enlargement, the risk of AUR appears to be high enough to justify intervention with a 5α-reductase inhibitor in order to reduce this risk.
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When discussing benign prostatic hyperplasia (BPH), it is imperative to carefully define terminology. Histologic BPH represents microscopic evidence of prostatic stromal and epithelial hyperplasia. In man, this proliferative process occurs exclusively in the transition zone and periurethral glands.[1] Macroscopic BPH represents the enlargement of the prostate arising from the stromal and epithelial proliferation. There is no consensus establishing the degree of prostate enlargement required to support the diagnosis of macroscopic

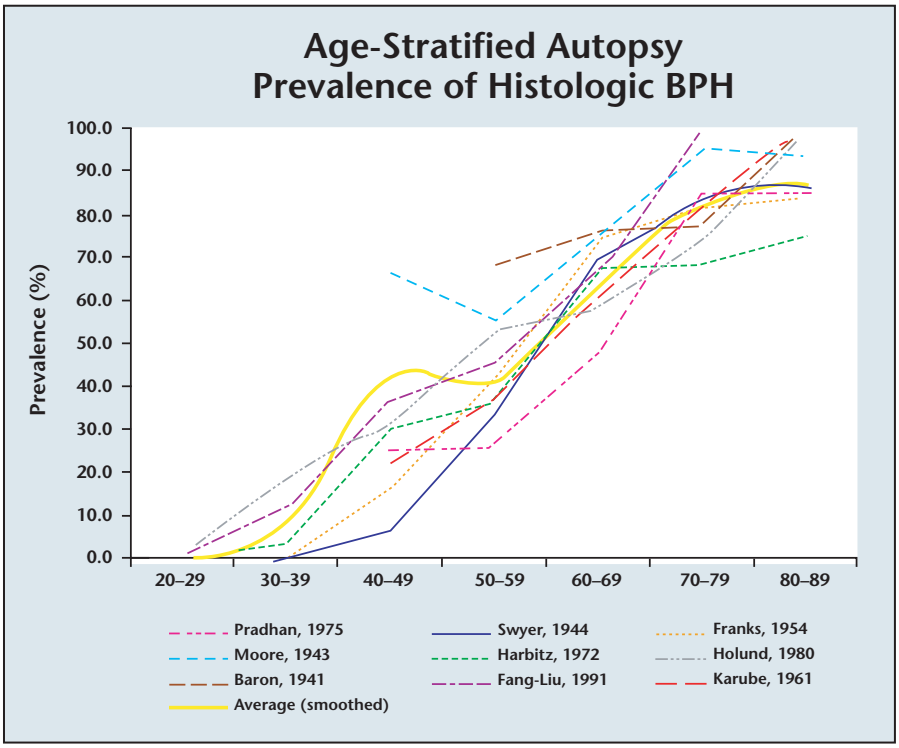

Figure 1. *Age-stratified autopsy prevalence of histologic benign prostatic hyperplasia (BPH). Reproduced with permission from Roehrborn CG, McConnell JD.*[4]

BPH. Clinical BPH represents the clinical manifestations attributed to the enlarged prostate. The clinical manifestations of an enlarged prostate include lower urinary tract symptoms (LUTS), bladder outlet obstruction, incomplete bladder emptying, acute and chronic urinary retention, urinary tract infection (UTI), urosepsis, bladder stones, and hematuria.[2] There are many urological and nonurological diagnoses other than an enlarged prostate that present with these symptoms including prostate cancer, prostatitis, bladder cancer, bladder stones, overactive bladder, interstitial cystitis, radiation cystitis, UTI, primary bladder neck hypertrophy, urethritis, diabetes, Parkinson's disease, lumbosacral disc disease, and multiple sclerosis. Often, clinical BPH is a diagnosis of exclusion once these other clinical entities have been ruled out.

Prevalence of Histologic BPH

The prevalence of histologic BPH can be determined only from autopsy studies. In 1984, Berry and colleagues[3] summarized 5 autopsy studies addressing the prevalence of histologic BPH according to age. Histologic BPH was never observed in men under the age of 30 years. Approximately half of men in the sixth decade of life exhibited histologic evidence of BPH. Almost 90% of men developed histologic BPH by the ninth decade of life (Figure 1). A review of the literature provides compelling evidence that the prevalence of histologic BPH is similar throughout the world.[4]

The specific factors that initiate and promote the proliferative process are unknown. The development of histologic BPH requires both aging and androgens.[5] Dihydrotestosterone (DHT) is the specific androgen mediating prostate development and growth. Testosterone is converted to DHT by the enzyme 5α-reductase (5AR). There are 2 subtypes of 5AR, Type 1 and Type 2. The primary subtype in the prostate is Type 2. Males with the 5AR deficiency syndrome do not convert intraprostatic testosterone to DHT.[6] Interestingly, males with this syndrome have rudimentary prostates as adults and do not develop BPH.[7] Males who are castrated early in life also fail to develop BPH.[8] Long-term treatment with the 5α-reductase inhibitors (5ARIs) dutasteride[9] and finasteride[10] not only causes some reduction of prostate volume but also prevents further growth of the prostate. The primary advantage of dutasteride is that it inhibits both 5AR subtypes, which results in a more complete suppression of DHT production. All of these observations demonstrate a pivotal role for androgens (DHT) in the development of the prostate and BPH. The observation that the growth of the prostate does not directly correlate with DHT levels[11] suggests that although DHT permits growth, factors other than the androgen milieu are responsible for the ultimate degree of prostatic enlargement.

Pathophysiology of BPH

Because the prevalence of histologic, macroscopic, and clinical BPH is age-related, it was often assumed that they were causally related.[12] This led to the hypothesis that the enlarged prostate was the cause of LUTS in the aging male population (Figure 2). Subsequent studies demonstrated that α-blockers and various pharmacologic strategies for achieving androgen suppression improved LUTS in men with BPH.[13] Alpha-blockers relax prostate smooth muscle tension[14] and hormonal therapy preferentially reduces epithelial volume.[15] On the basis of these clinical

observations and the proposed mechanism of action of these pharmacotherapies for BPH, it was assumed that α-blockers and hormonal therapy relieved LUTS by decreasing bladder outlet obstruction and shrinking the prostate, respectively. These clinical observations were interpreted to support the hypothesis that there are both dynamic and static components of bladder outlet obstruction associated with BPH (Figure 2).

The ability to ultimately prove or disprove the causal relationship between benign prostate enlargement, bladder outlet obstruction, and LUTS required the availability of noninvasive and reliable methods for assessing prostate volume, bladder outlet obstruction, and LUTS. It is well recognized that a digital rectal examination is an unreliable method for measuring prostate volume.[16] Prostate volume can be reliably measured using various imaging modalities including ultrasonography, magnetic resonance imaging, and computerized tomography. Computerized tomography and magnetic resonance imaging are extremely costly procedures. Transrectal ultrasonography has become the standard for quantifying the degree of prostate enlargement because the procedure can be performed in the outpatient setting.[17]

Lower urinary tract symptoms represent the most common clinical manifestation of BPH. The development of validated, self-administered, quantitative questionnaires capturing the severity of LUTS provided the opportunity to measure both baseline disease symptom severity and its response to treatment. Instruments such as the American Urological Association-Symptom Index (AUA-SI)[18] are now widely utilized to quantify the severity of LUTS in both clinical trials and clinical practice.

The accurate and reproducible measurement of bladder outlet obstruction requires sophisticated urodynamic equipment and an expertise in both performing and interpreting these studies. Because simultaneous pressure-flow urodynamic studies are costly and invasive, these studies have never been performed in a large cohort of men from the general community or those with BPH. Uroflowmetry has been accepted as a proxy for measuring of bladder outlet obstruction in clinical trials and clinical practice because it is noninvasive and less costly. The primary disadvantage of uroflowmetry is its lack of specificity for bladder outlet obstruction. For example, men with an acontractile bladder may have a low peak flow rate due to the inability to generate a significant detrusor contraction and not because of bladder outlet obstruction.

The Olmstead County Study of Urinary Symptoms and Health Status[19] provides important insights into the prevalence of LUTS, prostatic enlargement, and bladder outlet obstruction in the general community. In this study, 2115 men in Olmstead County, Minnesota between 40 and 79 years of age agreed to complete the AUA-SI and urinate into a home portable device to determine peak urinary flow rate. A subset of these men (approximately 25%) underwent prostate volume measurement using transrectal ultrasonography. The severity of LUTS, peak flow rate, and extent of prostate enlargement were all age-dependent. The proportion of men with moderate to severe LUTS (AUA symptom score ≥ 8), significant bladder outlet obstruction (peak flow rate ≤ 10 mL/sec), and markedly enlarged prostates (prostate volume > 50 cm^3) was also age-dependent. The R^2 values between AUA symptom score versus

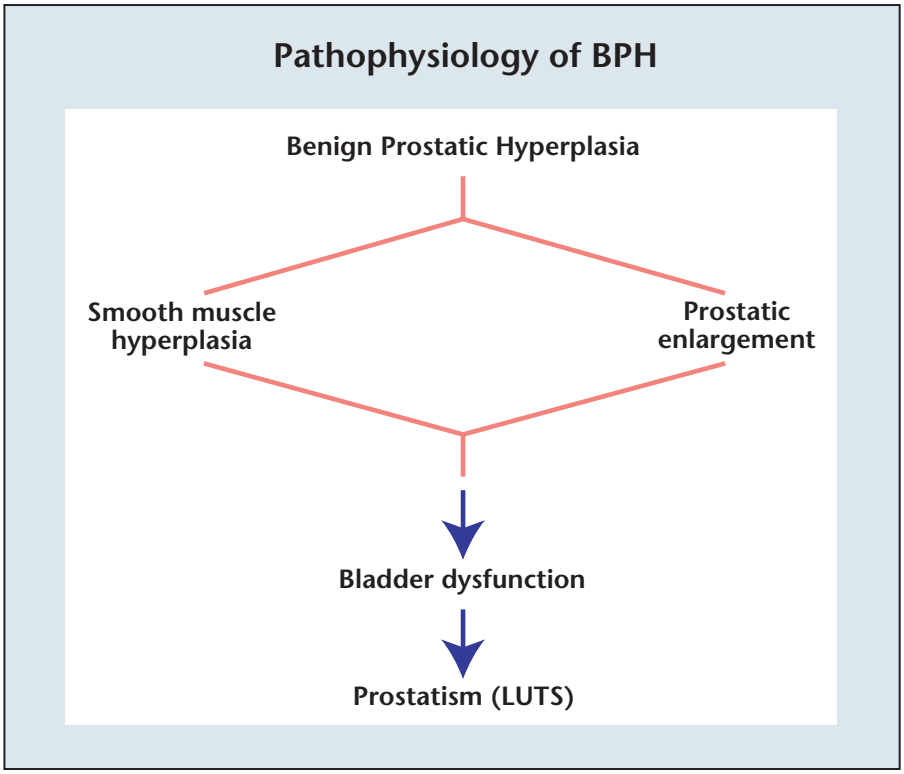

Figure 2. *Proposed pathophysiology of benign prostatic hyperplasia (BPH). A number of studies have challenged the paradigm that prostatic enlargement causes bladder outlet obstruction, leading to lower urinary tract symptoms (LUTS). Although BPH and bladder outlet obstruction clearly contribute to the development of LUTS, there are other unrecognized factors that also cause LUTS.*

prostate volume, peak urinary flow rate versus prostate volume, and AUA symptom score versus peak flow rate were .034, .057, and .123, respectively.

This suggests that only 3.4% of the variability in the AUA symptom score is attributable to prostate volume, 5.7% of the variability in peak flow rate is attributable to prostate volume, and 12.3% of the variability in the peak flow rate is attributable to AUA symptom score. These observations challenge the simplistic paradigm that prostatic enlargement causes bladder outlet obstruction that leads to LUTS (Figure 2). Whereas it is clear that an enlarged prostate and bladder outlet obstruction may contribute to LUTS, there are other unrecognized factors that also cause LUTS.

It is well recognized that both 5ARIs and α-blockers improve LUTS in men with BPH.[13] Lepor and colleagues[20] examined the outcomes of the Veterans Affairs Cooperative Study, which compared placebo, terazosin (an α-blocker), finasteride (a 5ARI), and combination therapy in order to gain insights into the mechanism for how these drugs improve LUTS. The R^2 value for the relationship between ΔAUA symptom score versus Δpeak urinary flow rate in the men receiving the α-blocker was not statistically significant. The R^2 value for the relationship between Δprostate volume and ΔAUA symptom score was also not statistically significant in those men receiving finasteride. These relationships suggest that α-blockers and 5ARIs may promote LUTS improvement through mechanisms other than relaxation of prostate smooth muscle and reduction of prostate volume, respectively.

The future challenge is not only to determine the precise mechanism by which α-blockers and 5ARIs improve LUTS, but also to identify other factors causing LUTS in the aging male.

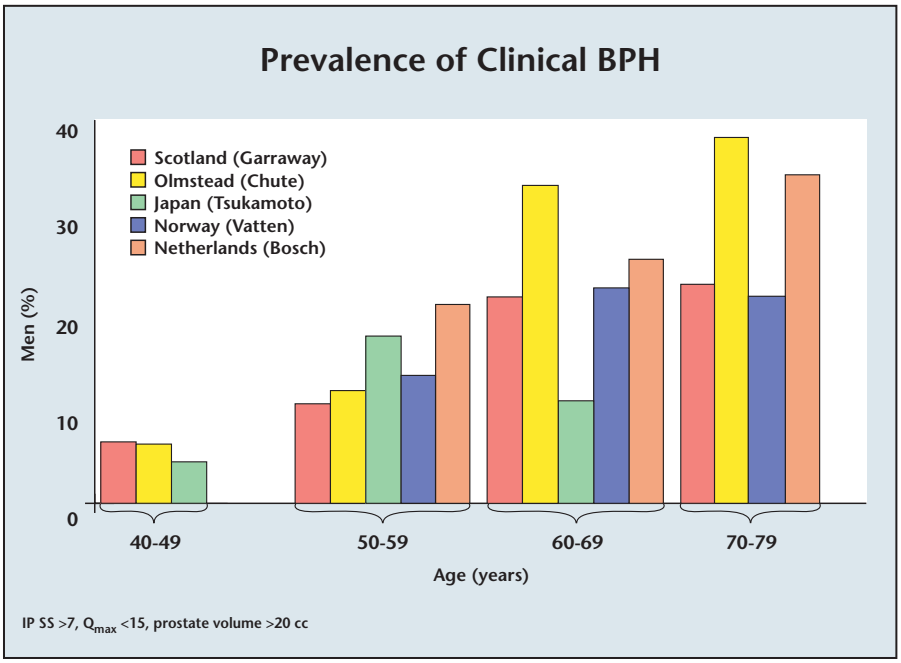

Figure 3. *Investigators in different countries have reported cross-sectional studies designed to determine the prevalence of clinical benign prostatic hyperplasia (BPH), as defined by an International Prostate Symptom Score (IPSS) > 7, peak urinary flow rate (Q_{max}) < 15 mL/sec, and prostate volume > 20 cc. The prevalence of BPH in these studies was consistently shown to be age-dependent, as well as fairly uniform across the world. Reproduced with permission from Roehrborn CG, McConnell JD.*[4]

These studies will likely provide insights into a next generation of pharmacologic strategies for the treatment of BPH.

Epidemiology

Historically, elucidating the epidemiology of BPH has been complicated by the lack of a uniform definition of clinical BPH, quantitative instruments for assessing LUTS severity, a noninvasive and accurate method for measuring prostate volume, and a noninvasive and accurate method for measuring bladder outlet obstruction. The development of self-administered quantitative indices for measuring the severity of LUTS, transrectal ultrasonography for accurately assessing prostate volume, and sophisticated instruments for performing simultaneous pressure-flow urodynamic studies now provides the opportunity to accurately define prevalence rates for these parameters in the general male community. Unfortunately, measuring both prostate volume with transrectal ultrasonography and bladder outlet obstruction with pressure-flow urodynamic devices is far too costly and invasive to perform in the general population. Another limitation related to determining prevalence rates for these parameters is that there is no consensus regarding what specifically constitutes an enlarged prostate or an obstructed bladder. It is unlikely that the prevalence rates for bladder outlet obstruction and prostate enlargement will ever be determined in the general community.

Men with prostate volumes > 50 cm^3 have a 5 times greater risk of having clinically moderate to severe LUTS and a 3 times greater risk of having significant bladder outlet obstruction, defined by a peak flow rate < 10 mL/sec. These observations suggest there is some relationship between prostate volume and both LUTS and obstruction, especially in

men with large prostates.

Several investigators in different countries have reported cross-sectional studies designed to determine the prevalence of clinical BPH (Figure 3).[21-24] Men in these studies were categorized as having clinical BPH if the International Prostate Symptom Score was ≥ 8, peak flow rate was < 15 mL/sec, and prostate volume was > 20 cm^3. This definition of clinical BPH shows the prevalence of the disease to be consistently age-related. The prevalence of clinical BPH is fairly uniform around the world.

Several factors have been reported to be associated with an increased risk for BPH including religion, socioeconomic factors, sexual activity, vasectomy, alcohol use, cirrhosis, hypertension, smoking, diet, and obesity. However, there is no compelling evidence that any of these factors is associated with a greater risk for developing BPH.[4]

Natural History

The natural history of a disease refers to the progression of the untreated disease over time. Clinical endpoints of progression for BPH include the development of more severe symptoms, bladder dysfunction manifested by incomplete emptying or detrusor instability, more severe bladder outlet obstruction, acute urinary retention (AUR), recurrent UTI, urosepsis, chronic renal insufficiency, bladder stones, incontinence, and hematuria. The natural history of BPH is incompletely understood because of the absence of a uniform definition of the disease and the lack of rigorous studies. Defining the natural history of BPH would require following a large cohort of men in the general community with symptom scores, transrectal ultrasonography, and pressure-flow urodynamic studies. Because these parameters are not necessarily causally related, the natural history of LUTS, bladder outlet obstruction, and prostatic enlargement should be independently examined. It is unlikely that such a study will ever be performed as conducting transrectal ultrasonography and pressure-flow urodynamic studies longitudinally in a cohort of healthy men would be prohibitively expensive and many asymptomatic men would be unwilling to subject themselves to these invasive tests.

The natural history of a disease can be inferred from the placebo arms of long-term intervention studies. The problem with this approach is that only men with established disease are included. It is also well recognized that those men volunteering for studies may not reflect the general community and that a clinical trial may influence behavior.[25]

Insights into the natural history of benign prostatic enlargement can be gleaned from the longitudinal follow-up of the Olmstead County Study of Urinary Symptoms and Health Status.[26] A relatively small subset of men between the ages of 40 and 79 were randomly selected from the Olmstead County community and underwent transrectal ultrasonography at baseline and 6 years later. A mixed-effects regression model showed that prostate volume increased by about 1.6% per year on average. Men with larger prostates at baseline experienced the greatest increase in prostatic volume. These findings are fairly consistent with cross-sectional studies, autopsy studies, and placebo arms of clinical trials. It is important to stress that patterns of growth at the individual level are highly variable.

Jacobsen and colleagues[27] reported on LUTS progression in the Olmstead County Study over an interval of 42

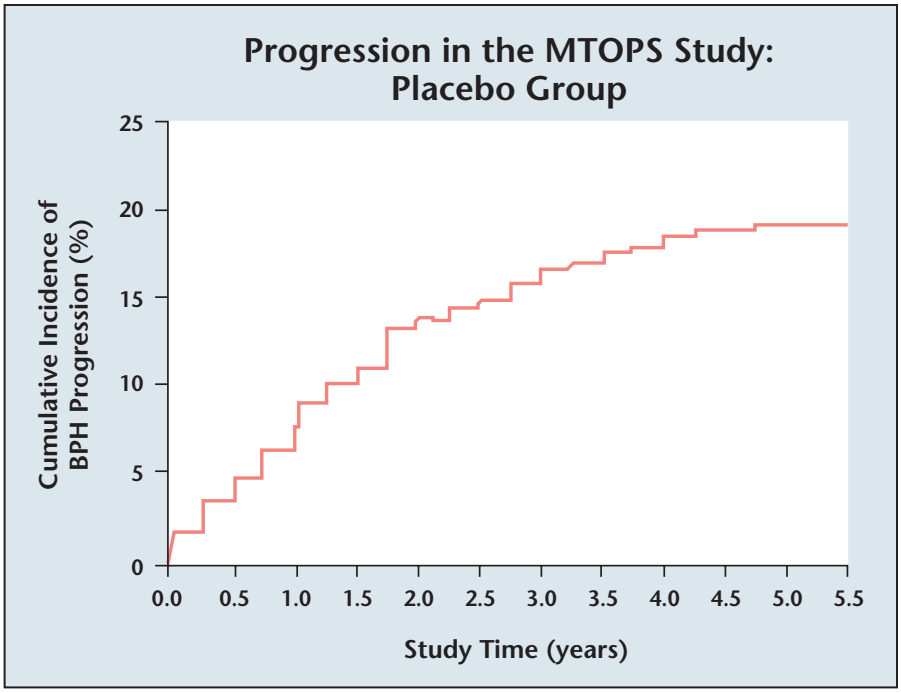

Figure 4. *The Medical Therapy of Prostatic Symptoms (MTOPS) study represents the longest placebo-controlled trial to date of men with benign prostatic hyperplasia (BPH). The placebo arm provides insights into the natural history of men with moderate to severe lower urinary tract symptoms and decreased peak urinary flow rates, which imply some level of bladder outlet obstruction. Adapted with permission from McConnell JD et al.[28] Copyright ©2003 Massachusetts Medical Society. All rights reserved.*

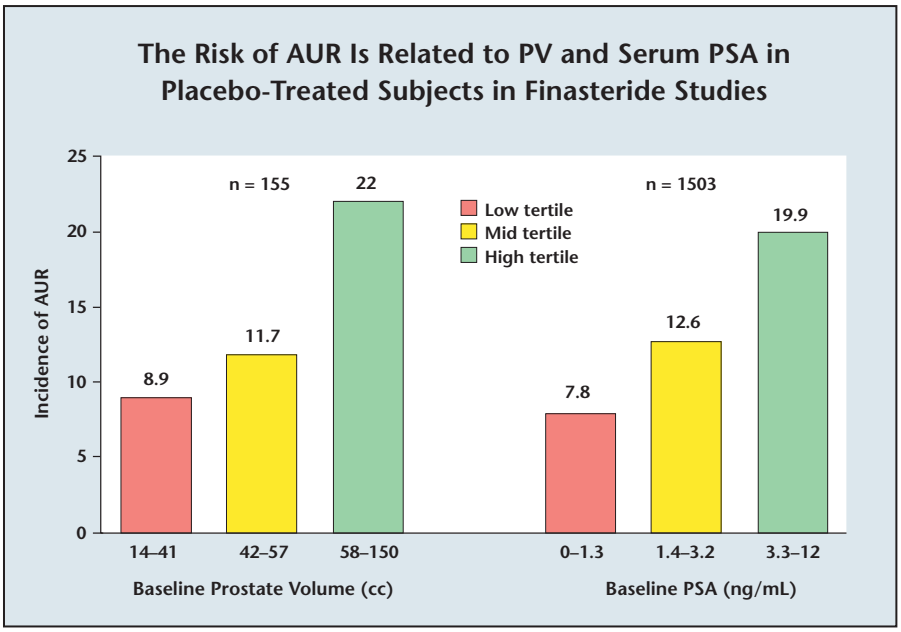

Figure 5. *The incidence of acute urinary retention (AUR) at 4 years among placebo-treated patients in finasteride clinical studies was clearly related to baseline prostate volume (PV) and prostate-specific antigen (PSA) levels. Adapted from Roehrborn CG et al.[32] with permission from Elsevier.*

months. The AUA symptom score was categorized as mild (0-7) versus moderate to severe (8-35). There was much movement across symptom categories during the follow-up interval. At 42 months, 22% of men with mild symptoms crossed over to moderate to severe symptoms. A

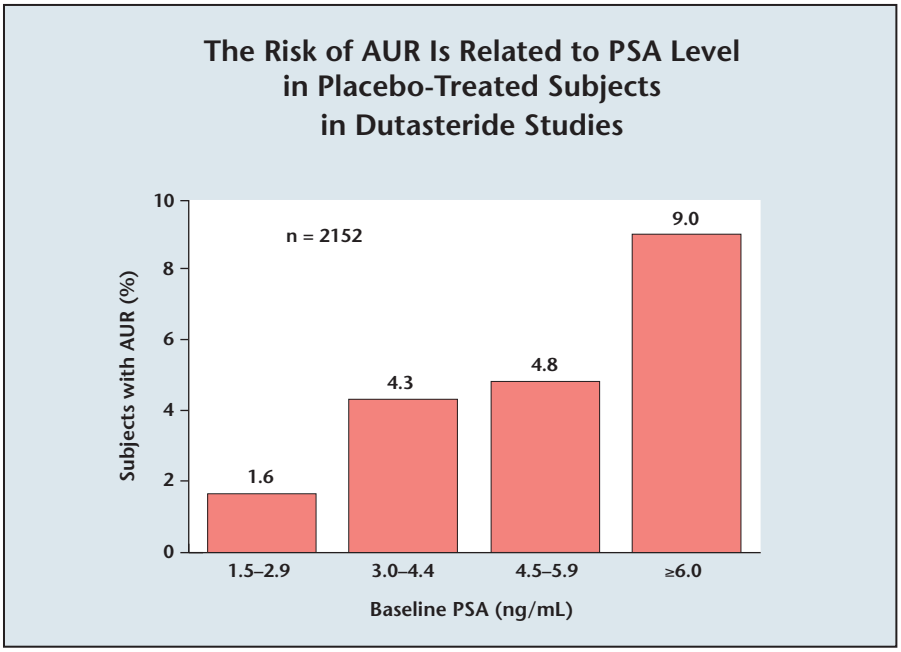

Figure 6. *The dutasteride clinical studies showed a clear relationship between baseline prostate-specific antigen (PSA) levels and the development of acute urinary retention (AUR) at 2 years in placebo-treated patients. Data from Roehrborn CG et al.[30]*

regression model showed that the average symptom score change over time was 0.18 symptom units per year. The AUA symptom score increased during this interval of time in all age categories. The greatest mean symptom score progression was observed in the 60- to 69-year-old age group.

The Medical Therapy of Prostatic Symptoms (MTOPS) study represents the longest placebo-controlled trial to date of men with BPH.[28] It is important to note that prostate volume was not an inclusion criterion for enrollment. Thus, the placebo arm provides insights into the natural history of men with moderate to severe LUTS and decreased peak urinary flow rates, which imply some level of bladder outlet obstruction. The objective of the MTOPS study was to examine the impact of medical therapies on BPH progression. In this study, BPH progression was defined as a 4-point increase in AUA symptom score or the development of AUR, chronic renal insufficiency or socially unacceptable incontinence, or recurrent UTI or urosepsis. The final analysis of the MTOPS study was recently conducted with a mean follow up of 4.5 years. The only clinically relevant progression rates were observed for symptom progression and AUR. The overall progression rate (events/100 patient-years) was 4.5 in the placebo group (Figure 4). The progression rates for symptom progression and the development of AUR were 3.6 and 0.6, respectively (Table 1). Subset analyses of the placebo group will be reported at a later time and should provide insights into the profile of men at greatest risk for progression.

The MTOPS study demonstrates that the development of AUR is quite common in men with clinical BPH. This is consistent with the Olmstead County Study of Urinary Symptoms

Table 1
Progression in the MTOPS Study Placebo Group
Placebo Treatment Group Progression Rate/100 Patient-Years

Clinical Progression	PLB
Overall	4.5
AUASS	3.6
AUR	0.6
Invasive Therapy	1.3

MTOPS, Medical Therapy of Prostatic Symptoms; PLB, placebo; AUASS, American Urological Association Symptom Score; AUR, acute urinary retention. Data from McConnell JD et al.[28]

and Health Status,[29] which reported a cumulative incidence rate for AUR of 6.8 per thousand person-years. With a multivariate analysis, age at baseline, symptom severity, and peak flow rate independently predicted risk of AUR. Prostate volume was not evaluable as a predictive factor as only a small subset of men underwent prostate volume determination at baseline. Based on information from the Olmstead County Study, a 60-year-old man with moderate to severe symptoms has a 13.7% chance of developing AUR by age 70.

The placebo arms of long-term studies evaluating the safety and effectiveness of the 5ARIs dutasteride[9,30] and finasteride[10] provide insights into the risk of AUR in men with LUTS, bladder outlet obstruction, and an enlarged prostate. In men with prostates over 58 cm^3, the risk of AUR in the finasteride study placebo group over the 4-year period was 22%.

It is not practical for the primary care physician to measure prostate volume using transrectal ultrasonography. Because benign prostatic hyperplastic tissue makes prostate-specific antigen (PSA), it is not surprising that there is a good correlation between prostate volume and serum PSA.[31] The risk of developing AUR can also be predicted from the baseline serum PSA level (Figures 5 and 6). Among men in the highest tertile baseline PSA in the finasteride placebo group (PSA ≥ 3.3 ng/mL), the risk of AUR at 4 years was 19.9%. Among men with a baseline PSA ≥ 6.0 ng/mL, the risk of AUR in the dutasteride placebo group at 2 years was 9.0%.

Controversy exists regarding the value of PSA-based screening to detect early prostate cancer. Despite this controversy, the majority of men over 50 years of age are undergoing PSA level testing in the United States. It is the author's opinion that the primary care physician should obtain a serum PSA level in men with clinical BPH. If the PSA level is elevated, a prostate biopsy should be recommended. The primary care physician should refer to Figure 6 in order to guide patients regarding the risk of AUR and the wisdom of intervening with a 5ARI in order to reduce this risk.

Conclusion

The pathophysiology, epidemiology, and natural history of BPH are incompletely understood. The development of reliable instruments to measure symptom severity, prostatic enlargement, and bladder outlet obstruction has allowed major advances in the elucidation of the pathophysiology, epidemiology, and natural history of the disease. The development of LUTS in the aging male population is influenced to some degree by the severity of bladder outlet obstruction and prostatic enlargement. It is important to recognize that many other factors unrelated to bladder outlet obstruction

Main Points

- There is no consensus as to the degree of prostate enlargement required to support a diagnosis of benign prostatic hyperplasia (BPH). Histologic evidence of BPH can be determined only from autopsy studies. The clinical manifestations of BPH are present in a number of other urological and nonurological disease states.
- The specific factors that initiate and promote the proliferative process are unknown. The development of histologic BPH requires both aging and androgens. Although dihydrotestosterone (DHT) is the specific androgen mediating prostate development and growth, there is no direct correlation between DHT levels and prostate growth.
- Lower urinary tract symptoms (LUTS) are the most common clinical manifestation of BPH. Men with prostate volumes > 50 cm^3 have a 5 times greater risk of having clinically moderate to severe LUTS and a 3 times greater risk of having significant bladder outlet obstruction, suggesting that there is a relationship between prostate volume and both LUTS and obstruction. Because there is a strong correlation between prostate volume and prostate-specific antigen (PSA) levels, the risk of developing acute urinary retention (AUR) can be predicted from baseline PSA levels. There are, however, many other factors involved in the pathophysiology of LUTS.
- The natural history of BPH is highly variable at the individual level. The clinically important parameters of disease progression in men with moderate to severe LUTS and low peak flow rates are symptom progression and the development of AUR. In men with moderate prostate enlargement, the risk of AUR appears to be high enough to justify intervention with 5α-reductase inhibitors in order to reduce this risk.

and prostatic enlargement are involved in the pathophysiology of LUTS. Although the development of LUTS, bladder outlet obstruction, and benign prostatic enlargement are age-dependent, they are not necessarily causally related. The natural histories of these parameters are highly variable at the individual level. The clinically important parameters of disease progression in men with moderate to severe LUTS and low peak flow rates are symptom progression and the development of AUR. The risk of AUR is related to both baseline serum PSA level and prostate volume. In men with moderate prostate enlargement, the risk of AUR appears to be high enough to justify intervention with 5ARIs in order to reduce this risk. ■

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